REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 22, 23, 27-33, 47-66, 69, 71-79, and 82-85 were pending in this application when last examined.

Claims 66, 69, 71-79, and 85 were examined on the merits and stand rejected.

Claims 22, 23, 27-33, 47-65, and 82-84 were withdrawn as non-elected subject matter.

Claim 66 is amended to clarify how expression of the identified polynucleotide(s) from the patient sample indicates disease. Support can be found in the disclosure, for example, at page 10, lines 16-20, page 24, lines 10-14, and claim 66 as filed.

Claims 66 and 69 are amended to clarify the source of the patient and reference samples. Support can be found in the disclosure, for example, page 65, lines 5-8; page 68, lines 22-26; Figures 1-2, page 23, lines 20-21; page 23, lines 27-28; page 24, lines 6-9; Figure 6 on page 83, lines 16-30, page 84, lines 1-2; Example 5 on pages 96-97 and page 98, lines 1-9; Example 6 on page 98, lines 26-30 and pages 99, 100 and 101, pages 1-9.

Claims 74 and 76 are amended to clarify the nature of "the tissue from an organ other than liver but that is subject to cancerous transformation." Support can be found in the disclosure, for example, at page 15, lines 10-11.

Claim 79 was revised to remove an extra comma after "wherein" in line 1.

No new matter has been added by the above amendments.

Claims 22, 23, 27-33, 47-66, 69, 71-79, and 82-85 remain pending upon entry of this amendment.

II. UNEXAMINED SUBJECT MATTER

On pages 2-3 of the Office Action, it was again indicated that claims 66, 67 and 69-80 encompass unelected inventions drawn to detecting sequences (i.e., unelected sequences of SEQ

ID NOS: 12-19) other than elected SEQ ID NO: 11.

In the last response, Applicants discussed the significance of the present invention in the detection of a nucleic acid sequence of SEQ ID NO: 11 alone or in combination with the non-elected sequences of SEQ ID NOS: 12-19. In the last response, Applicants also requested the Office to examine the unelected sequences in combination with the elected sequence.

The Office acknowledged the importance of the combination of sequences in the invention. However, the Office maintained that it will not examine non-elected sequences until the broad method claims to elected SEQ ID NO: 11 are found allowable.

Accordingly, Applicants respectfully request the Office to examine the non-elected sequences with the elected sequence upon an indication of allowance of the broad method claims to elected SEQ ID NO: 11.

III. INDEFINITENESS REJECTION

On pages 3-4 of the Office Action, claim 66 was again rejected under 35 U.S.C. § 112, second paragraph, as indefinite on the basis that it is unclear how over-expression of the identified polynucleotide(s) as compared to the reference library or reference sample is indicative of a diagnosis of hepatocyte carcinoma.

This rejection is respectfully traversed as applied to the amended claims.

Claim 66 was amended along the lines suggested by the Office to include a correlation step to clarify how over-expression of the identified polynucleotide(s) in the sample from the patient indicates that said patient has hepatocellular carcinoma. Support can be found in the disclosure, for example, at page 10, lines 16-20, page 24, lines 10-14, and claim 66 as filed. As demonstrated in the examples in the specification, over-expression of the identified polynucleotide(s) in the sample from the patient correlates to elevated expression in the blood sample as compared to that of the control. This over-expression as compared to the control indicates a diagnosis that said patient has hepatocellular carcinoma. One skilled in the art, upon reading the disclosure and in view of the knowledge in the art, would clearly understand the metes and bounds of such language.

For this reason, the above-noted indefiniteness rejection is untenable and should be withdrawn.

IV. ENABLEMENT REJECTION

On pages 5-6 of the Office Action, claims 66 and 85 were again rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification lacks enablement for the full scope of the claims. The Office considered the arguments in the last response to be unpersuasive. Specifically, the Office argued that one of skill in the art would not predict SEQ ID NO: 11 expression in just any patient and control sample to function in the claimed method with an expectation of success.

Applicants respectfully traverse this rejection for the reasons set forth in the response filed May 9, 2007 and for the following reasons.

To start, the Office objected to an allegedly insufficient disclosure for a method of diagnosing HCC by using any type of patient compared to just any type of sample or just of any type of reference library or any other sample. The Office proposed limiting the blood sample for both the patient and reference samples.

Applicants respectfully disagree with the Office's position and proposed limitations for the reasons set forth in the arguments already submitted in the response filed May 9, 2007. Applicants herein reiterate the arguments in the response filed May 9, 2007.

Again, as argued in the previous response, the specification demonstrates that overall, DNA chip, RT-PCR and immunohistochemistry (IHC) data show highly specific up-regulation of RNA of SEQ ID 11 in patient samples derived from hepatocellullar carcinoma (HCCs) livers as compared to reference library/sample represented by RNA isolated from normal liver (non-neoplastic) or other neoplastic tissues. Namely, the mean RNA expression level for SEQ ID No. 11 exceed all other normal and neoplastic tissues tested at least by factor 8. See for example, Figures 1-2, page 23, lines 20-21. The quantitative RT-PCR results mirror the cDNA microarray data. See page 23, lines 27-28. *In situ* hybridization reveals the specific and strong expression of SEQ ID No. 11 RNA in cytoplasm of cells derived from HCC tissue, whereas it is not detected in

tumor stroma and non-neoplastic liver cells. See page 24, lines 6-9.

In the siRNA mediated knock down of SEQ ID 11 expression in the hepatocellular carcinoma cell line (HepG2 cells), it is determined that the level of mRNA encoding the tumor suppressor gene retinoblastoma protein 1 (RB1) is up-regulated several fold, in a dose dependent manner. See Figure 6 on page 83, lines 16-30, page 84, line 1-2; Example 5 on pages 96 to 97 and the page 98, lines 1-9.

It is again respectfully submitted that such data in the instant specification support the role of SEQ ID No. 11 in detection (and treatment) of hepatocellular carcinoma, wherein the over-expression/elevated expression of SEQ ID No. 11 RNA may provide a negative regulation of the RB1 and therefore facilitate tumor cell growth.

Furthermore, based on the experimental set up of Example 6 (page 98 lines 26-30 and pages 99, 100 and 101 lines 1-9 of the disclosure), Applicants have performed RT PCR approach to detect upregulation of SEQ ID 11cDNA in blood of HCC patients. See again the discussion in the attached Appendix 1, which was submitted with a previous response filed October 16, 2007.

The above mentioned data provide the evidence of a specific upregulation of SEQ ID 11 in the patient sample isolated from (a) liver tissue, i.e. DNA chip array, RT-PCR or IHC, (b) liver cell, i.e. siRNA knock down, or (c) blood, i.e. RT PCR by using HCC blood samples , when compared to reference sample represented again by liver tissue, non transformed liver cells or blood from the control.

Accordingly, Applicants have amended terms "patient/ reference samples" in claims 66 and 69 based on limitations of dependent claims 74 and 76 to "liver tissue, a liver cell, blood, serum, plasma" to be consistent with the disclosure.

In regard of serum and plasma (fractions of blood) it is well know in art field that:

(a) serum is defined as a blood plasma without fibrinogen and other clotting factors), and

(b) plasma is a straw-colored liquid in which the blood cells are suspended).

Such definitions can be found on the web at http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/B/Blood.html.

Further, Applicants also note Panzitt et al., Gastroenterology, Vol. 132, No. 1, pp. 330-342 (2007) attached to the response filed May 9, 2007. This reference is further evidence that the instant disclosure is enabling for the claimed invention of detecting hepatocellular carcinoma. Again, the authors of this paper include the Applicants. Panzitt et al. is related to characterization of the SEQ ID NO: 11 ("HULC") gene. The authors found that this novel gene is involved in striking over-expression/up-regulation in hepatocellular carcinoma, as non-coding RNA. They found that this gene (i.e., HULC = the present invention) is the most over-expressed/up-regulated gene in HCC and was detected in blood of HCC patients. The results of the paper are evidenced concluded that the gene is useful as a novel biomarker for HCC. See the abstract of Panzitt et al.

Based on the guidance and working examples in the disclosure in view of the knowledge in the art field as evidenced by Panzitt et al., it is respectfully submitted that skilled artisan would reasonably believe that the specification is enabling for the claimed method of detection.

Therefore, the 112, first paragraph, enablement rejection of claims 66, 67 and 70-80 is untenable and should be withdrawn.

V. ANTICIPATION REJECTION

On pages 6-9 of the Office Action, claims 66, 69, and 71-79 were again rejected under 35 U.S.C. § 102(b) as anticipated by Horne et al. (WO 02/29103 A2; 4/11/02).

The Examiner again argues that Applicants are arguing limitations not in the claims. Specifically, the Examiner notes the pending claims do not require SEQ ID NO: 11 to be up-regulated in hepatocellular carcinoma samples as compared to control. The Examiner notes claim 66 only requires that over-expression of SEQ ID NO: 11 as compared to a non-disease control is indicative of a diagnosis of hepatocellular carcinoma.

The present amendment overcomes this rejection.

Based on the statements on page 17 of the Action, it appears the Office maintained the rejection on the basis that Applicants are arguing limitations not in the claims. For instance, on page 17, it was indicated that "the claims are not drawn to a specific diagnosis of hepatocyte

carcinoma."

First, in reply thereto, please note the amended claims are drawn to a specific diagnosis of hepatocellular carcinoma. In particular, amended claim 66 calls for a method of diagnosing-hepatocellular carcinoma, said method comprising:

(1) identifying a polynucleotide in a sample from a patient, wherein said polynucleotide is a polynucleotide consisting of the polynucleotide sequence of SEQ ID No. 11 or a polynucleotide comprising the polynucleotide sequence of SEQ ID No. 11,

alone or in combination with at least one polynucleotide consisting of a polynucleotide sequence selected from SEQ ID Nos. 12-19 or a polynucleotide comprising the polynucleotide sequence selected from SEQ ID Nos. 12-19, and

(2) comparing expression of the polynucleotide(s) identified in step (1) with expression of said polynucleotide from a non-diseased control, wherein over-expression of the identified polynucleotide(s) as compared to the non-diseased control is indicative of a diagnosis of hepatocellular carcinoma.

Horne (WO 02/29103) fails to teach this specific method of diagnosis, including all of the recited method steps.

Second, as noted in the last response, Applicants again respectfully note that the claims call for methods which require using a "polynucleotide consisting of the polynucleotide sequence of SEQ ID No. 11 or a polynucleotide comprising the polynucleotide sequence of SEQ ID No. 11" and diagnosis by detecting up-regulation.

Again, Horne fails to disclose or suggest this sequence. Instead, Horne discloses a polynucleotide sequence SEQ #2645 (which shares 95.6% homology to Exon 2 region of clones 5 = SEQ ID No. 11). This sequence (sharing 95.6% homology) is not the same sequence consisting of SEQ ID NO: 11. Therefore, Horne fails to teach each and every element of the claimed invention. For this reason, Horne fails to anticipate the claimed invention.

Third, as noted in the last response, the sequence in Horne is disclosed to be down-regulated in metastatic malignant liver (secondary liver cancer). This means that the polynucleotide sequence SEQ #2645 in Horne exhibits the opposite expression pattern compared

to elected SEQ ID NO: 11 of the present invention, which is highly over-expressed/up-regulated in HCC (primary liver cancer) (see page 23, line 29 to page 24, line 14 of the instant disclosure). Thus, it is again respectfully submitted that the sequence in Horne is related to a different peptide than the claimed invention and it is related to a different form of cancer than that of the claimed invention.

As a result, in contrast to the present invention, sequence SEQ #2645 in Horne is not an optimal hepatocellular carcinoma biomarker. There is no suggestion in Horne to use this sequence for such. In fact, the skilled artisan would not use the sequence in Horne in the claimed method, because the Horne sequence would not be involved in up-regulation, i.e., over-expression, in hepatocellular carcinoma, as required by the claimed method. Consequently, the skilled artisan would not select the sequence in Horne (listed among other more than 800 ESTs and genes showing various pattern in primary or secondary liver cancers) to be used in the claimed method, because it not an optimal HCC biomarker involved in up-regulation or over-expression. For this reason, Horne fails to disclose each and every element of the claimed invention. Therefore, Horne fails to anticipate the present invention.

In view of the above, the rejection of claims 24, 25 and 34-45 under 35 U.S.C. § 102(b) as anticipated by Horne (WO 02/29103) is untenable and should be withdrawn.

VI. CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested. If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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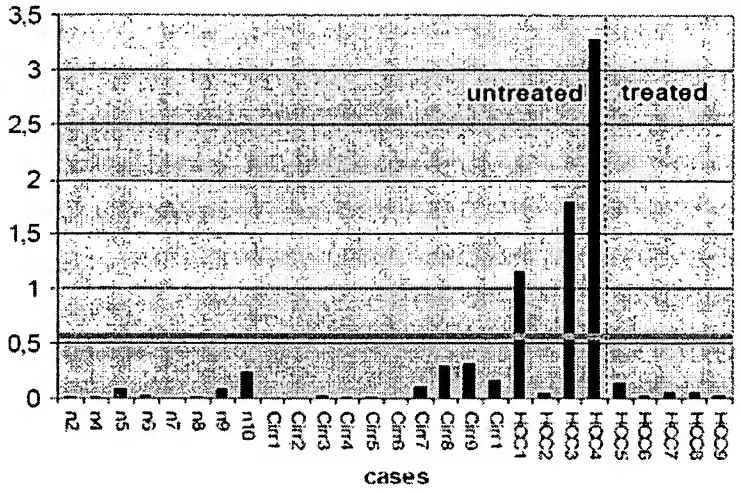
ATTACHMENT

1. Appendix 1 attached to the response dated October 16, 2007.

APPENDIX 1 to the communication dated October 16, 2007

HULC ncRNA in blood



Detection of HULC RNA in peripheral blood by light cycler RT-PCR assay. Peripheral blood cell were analysed from 9 normal subjects (n2-10), 10 patients with liver cirrhosis (Cirr 1-10), and 9 patients with HCC (HCC 1-9). Note that HCC patients 1-4 were analysed before any treatment, whereas patients 5-9 were analysed after successful chemoembolization. Alpha fetoprotein levels determined in parallel in HCC patients was only clearly positive in patient HCC4. Values at the left indicate ratios of HULC/ß-actin RNA concentrations in a log2 scale.

Most importantly from the standpoint of the invention, the data provide evidence that HULC RNA is readily detectable in the CTC-enriched fraction of blood from HCC patients. Levels in the blood of healthy volunteers and patients with cirrhosis in contrast are significantly lower. Since liver cells would not be expected to be shed by healthy people and by cirrhosis patients these lower levels most likely represent "noise". HULC levels above a certain threshold – (here arbitrarily set at 0.6 but requiring analysis of further samples) could therefore be diagnostic of liver cancer.

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